ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

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research news

Fighting the devastation of stroke

On the Cover

Sander Sarioglu is entering his fourth year of graphic design and illustration at the Alberta College of Art & Design in Calgary. He enjoys working in any and all mediums. The cover piece was done in watercolour and ink.

AHFMR Mission

AHFMR supports a community of researchers who generate knowledge whose application improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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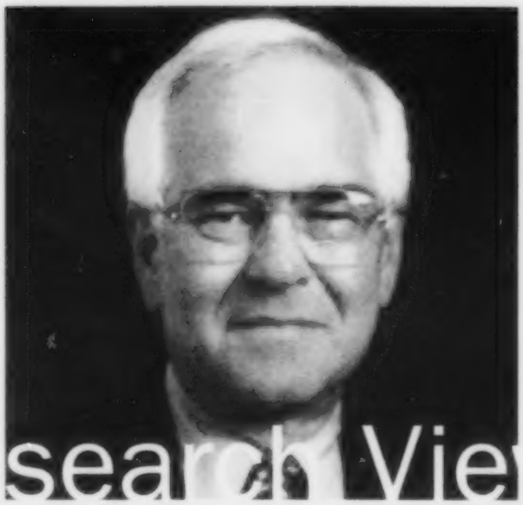


July 5, 2004 ushered in a new era of leadership for AHFMR when Dr. Kevin Keough officially took the reins as President and CEO.

Dr. Keough brings a wealth of experience in research, administration, and policy-making to AHFMR. Born in Newfoundland, he was for many years a professor of biochemistry at Memorial University in St. John's, and served as Memorial's first vice-president of Research and International Relations. Dr. Keough also played a key role in the formation of the Canadian Institutes of Health Research (CIHR), both in discussions leading to its creation and as a member of its interim governing council. Most recently, he was Health Canada's first Chief Scientist, a position he held in Ottawa while maintaining an active research lab at Memorial University.

"As Chief Scientist, I provided Health Canada with advice about how science informs policy; about science policy in health care; about the standards, conduct, and funding of science; and how it's used," says Dr. Keough. "I very much enjoyed what I was doing, but AHFMR and the opportunity it presented to make a difference in another milieu really appealed to me. It was just too good an opportunity to turn down.

"AHFMR was just too good an opportunity to turn down."

"I've always considered AHFMR an inspired, innovative move on the part of Peter Lougheed and his colleagues," he says, referring to the Foundation's birth in 1980. "It is regarded with envy across the country. It has been highly successful and continues to have great potential. So I was really excited about the possibility of joining the Foundation.

"I know I have big boots to fill," says Dr. Keough, adding that he has known predecessor Dr. Matthew Spence for over 30 years, dating back to Dr. Keough's days as a grad student, and including their work together on the creation of CIHR and other projects. "The previous two presidents have accomplished a great deal. I want to spend some time talking to the community, the Board, the stakeholders, the partners in Alberta and elsewhere, the science advisory committees, and of course the International Board of Review, which has just completed its job. My vision for AHFMR will be guided by that kind of input. I can tell you that it will include a broad perspective on health research, and it will include the two keystones that I think have made AHFMR so successful: its concentration on excellence and its concentration on people. Because it is the intelligence and imagination of people that eventually makes a difference in science."

AHFMR's success is based on excellence and people

Meanwhile, winding down his own research activities at Memorial in order to assume his responsibilities at AHFMR has been a difficult step for Dr. Keough. "I am invigorated by science; it has been a part of my life for a long time," he says of the role the lab has played in his life. "But with AHFMR, I plan to continue to be invigorated by science, just in a different way."

Dr. Keough's combination of experience seems to give him an ideal background to guide AHFMR. "I understand the challenges facing the researchers and the funding agencies. Having been a researcher and an administrator and having worked with CIHR, I've been through the spectrum to some extent. And having spent the last three years inside government, I understand some additional perspectives in terms of bureaucratic and political challenges." However, he expects he will still have a great deal to learn. After 32 years in Newfoundland, moving to Alberta and AHFMR will present new challenges. "That is where I'll hit a steep learning curve," he admits, "but I'm looking forward to it."

ABOVE: DR. KEVIN KEOUGH

Regulating calcium

More than twenty years ago, when Gary and Margaret Kargacin met in a German class at the University of Washington in Seattle, their lives were about to change in many ways. Not only did they later marry, move to Canada, and become parents, they also ended up working in complementary research areas.

The Kargacins, both members of the Smooth Muscle Research Group at the University of Calgary, are researching the role of calcium in muscle contraction. "It actually works out pretty well," says Dr. Margaret Kargacin. "We have our own separate projects, but then we collaborate on a lot of things too."

"The questions we ask are pretty fundamental and have a broad applicability," says Dr. Gary Kargacin. "The basic information that we're obtaining is important. It may not show its full significance for many years, but it's important to have this ongoing basic research."

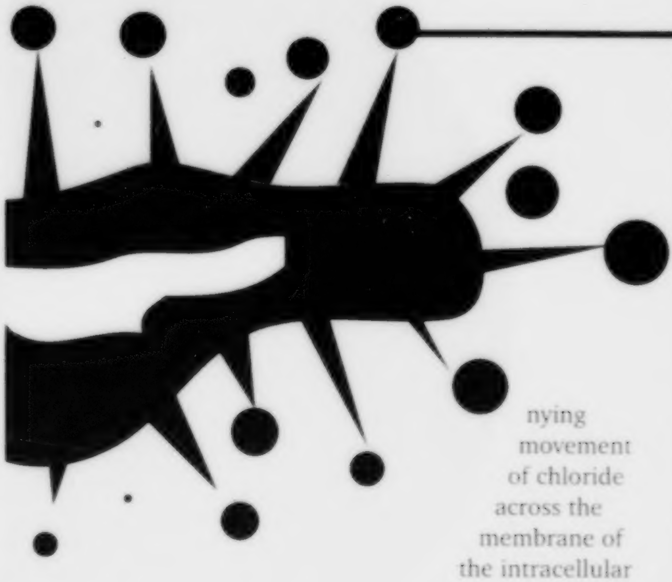
LEFT: DRS. MARGARET AND GARY KARGACIN

The Kargacins are interested in how the uptake and release of calcium is regulated in muscle cells, particularly the mechanisms by which calcium is removed from inside muscle cells (skeletal, cardiac, and smooth muscle).

All muscles require an increase in calcium as a signal for contraction, he explains. "The calcium in smooth muscle can come partly from intracellular storage sites and partly from outside the cell. In skeletal muscle, it comes entirely from storage sites inside the cell. In cardiac muscle, a little comes from the outside, and most of it comes from the inside. In order for a cell to contract, the calcium has to increase. For it to relax again after the contraction is complete, the calcium needs to be removed from the cell."

The Kargacins investigate calcium cell signaling.

The Kargacins and their colleagues are investigating calcium cell signalling and the role that "calcium pumps" play in regulating contraction in smooth-muscle cells. Their research has already significantly increased knowledge of how cells work and how calcium movement is regulated. For instance, their research on tamoxifen (a drug used to treat and prevent breast cancer) has led to an increased understanding of its actions and may improve understanding of some side effects associated with its use. The Kargacins have discovered that tamoxifen can inhibit the transport of calcium into the intracellular storage sites of cardiac muscle. They believe that it does so by blocking an accompa-



nying movement of chloride across the membrane of the intracellular storage sites.

The Kargacins are also researching the localization of proteins in cardiac and smooth muscle. In some diseases there's an alteration in the way that the proteins function, where they are located, and/or the amounts of some proteins in the muscle cell.

Gary has created computerized one- and two-dimensional models of the regulation of calcium in smooth-muscle cells. These models are helping answer questions about how calcium affects cell function. The Kargacins are also using the models to study microenvironments within the cell itself. "Cells may have areas that function differently from one part to another," explains Margaret. "It's fascinating."

Dr. Gary Kargacin is an associate professor in the Department of Physiology and Biophysics at the University of Calgary. He receives funding from the Canadian Institutes of Health Research (CIHR) and the Heart and Stroke Foundation of Alberta.

Dr. Margaret Kargacin is a research associate professor in the Department of Physiology and Biophysics and receives CIHR funding.

Selected publication

Kargacin ME, Zenobia A, Ward CA, Pollock NS, Kargacin GJ. Tamoxifen inhibits Ca2+ uptake by the cardiac sarcoplasmic reticulum. *European Journal of Physiology* 2000 Jul;440(4):573-579.

Dr. Rick Wozniak studies communication—not the kind that goes on between people and computers, but communication within the microscopic world of the cell.

Cell communication

Communication is all about sending information to various places to get things done, says the Heritage Senior Scholar; and transportation of proteins within a cell is a form of communication. Using the techniques of molecular biology, Dr. Wozniak's laboratory is unravelling the mystery of how the cell nucleus (the part of the cell that contains its DNA) communicates with the rest of the cell and the outside world. In particular, his lab investigates how thousands of nuclear pore complexes (gateways in the nuclear membrane) control the movement of proteins into the nucleus. In their work with both yeast cells and animal cells, Dr. Wozniak's team have discovered that the pore complexes select which proteins cross the membrane into the nucleus, and that they even control the timing of this protein movement.

For a cell to lead a healthy existence, proteins need to get to the right place in a cell and function properly when they get there. Diseases such as cystic fibrosis and cancer develop when normal protein transport goes awry. "In order for us to understand and intelligently treat problems with cells, which manifest themselves as diseases, we need to understand how the cell works," says Dr. Wozniak. "And that understanding is really the mandate of basic research."

Transportation of proteins within a cell is a form of communication.

The regulation of proteins in and out of the cell nucleus affects cell division and gene expression. Dr. Wozniak's team has shown that it is possible to slow cell division by altering the transport processes at the level of the pore complexes. Since cancers arise from rapidly dividing cells, slowing the

division of cells through these complexes may one day have implications for treating cancers, or at least slowing their progression.

"Science is building blocks," says Dr. Wozniak, explaining the importance of the basic research he conducts—research that is years away from practical application. "Some blocks are a lot bigger than others, but it's all about putting this together one piece at a time. And as we put those pieces together, the foundation becomes bigger, providing more and more avenues for future discoveries."

As an undergraduate science student at Michigan State University (MSU) in the late 1970s and early 1980s, Dr. Wozniak dreamed of getting into veterinary medicine—until his last year of studies, when he started doing research in a biochemistry lab. He was so excited by what was happening in molecular cell biology at the time that, instead of applying only to MSU's college of veterinary medicine, he applied also to graduate programs in cell biology. While being interviewed at New York City's Rockefeller University in 1981, he met with two prominent cell biologists—Nobel Prize winner Dr. Christian de Duve and Dr. Günter Blobel. Realizing he was being offered the chance of a lifetime, Dr. Wozniak chose Rockefeller's graduate program over veterinary medicine and has never looked back.

Rick Wozniak worked as a graduate student with Dr. Blobel, and then as a post-doctoral fellow. "I can remember vividly the first time I talked to him for any length of time," he recalls. "We spent three hours talking about protein trafficking: what was known and what wasn't known. I was just blown away by this guy." Dr. Blobel went on to win the 1999 Nobel Prize for physiology and medicine, for discovering that proteins have intrinsic "ZIP code" signals that govern their transport and localization in the cell.

"There are few people I've ever met in science that have the ability to communicate a passion for the subject the way he does," Dr. Wozniak says of Dr. Blobel. "That is so important because one of the things about doing science is that there's no instant gratification in this business. You've got to really hang with it for the long haul. You can sometimes go a year without getting any results that are important, and you can struggle. So you really have to have somebody there who can communicate excitement to you when you're down, and who can keep you motivated. He was great at that because he had such a passion for what he did.

"What we do with our science will endure."

"One of the most important lessons that I learned at Rockefeller—other than all the science—was that if you want to motivate people to do their best, you communicate the passion you have for what you do."

Since arriving at the University of Alberta in 1994, Dr. Wozniak has used his own passion for basic research to help drive his research program forward, and he is well on his way to leaving his own mark. "You get a feeling sometimes, when you make a discovery or you see something new, that you're placing yourself in some small way into the annals of science," says Dr. Wozniak. "As scientists, we can, through the success of our research, leave our mark on society. What we do with our science will endure as an important part of our legacy as individuals."

Heritage Scientist Dr. Rick Wozniak is a professor in the Department of Cell Biology at the University of Alberta. He also receives funding from the Canadian Institutes of Health Research.

Selected publication

Makhnevych T, Lusk CP, Anderson AM, Aitchison JD, Wozniak RW. Cell cycle regulated transport controlled by alterations in the nuclear pore complex. *Cell* 2003 Dec 26;115(7):813-823.

ABOVE: DR. RICK WOZNIAK

Will you be *safe* in the woods *today?*

If you go down in the woods today, you're sure of a big surprise.

– J.Kennedy, "The Teddy Bears' Picnic"

If you were to go into the woods today—in some areas of North America, at least—you actually could be in for a surprise, an unpleasant surprise. Anyone who enjoys such outdoor activities as hiking, hunting, and climbing is at risk of being bitten by ticks in woods or rural areas. These tiny bloodsucking parasites can do you a lot of harm. In parts of southern Ontario and across the United States some ticks are infected with a type of bacteria that can make you quite ill. The tick picks up the bacteria when it feeds on an infected mouse or other small rodent, and it passes this germ (known as *Borrelia burgdorferi*) to you while attached and feeding. The bacteria enter your bloodstream at the site of the tick bite and begin to multiply in the body. They travel via the bloodstream to different parts of the body and can produce Lyme disease, a disorder that causes fever and often a rash at the site of entry. Lyme disease is the most common insect-transmitted disease in North America.

If not properly diagnosed and treated, Lyme disease can affect the joints, the nervous system, the heart, and the skin. In some cases, infected individuals develop arthritis; less commonly, heart abnormalities, meningitis, or Bell's palsy (a condition that results in weakness or paralysis of the facial muscles).

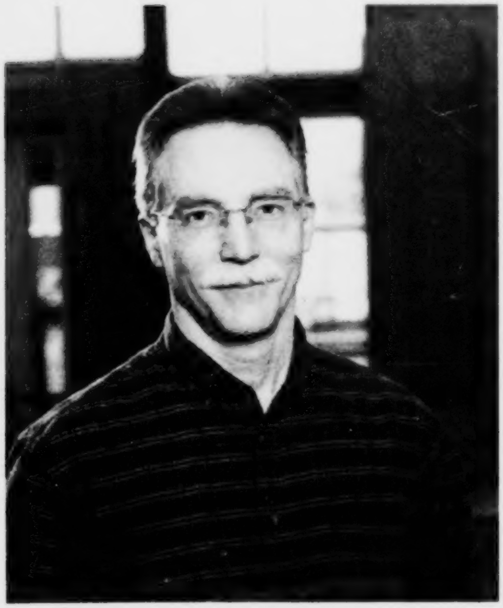
The good news...

Fortunately, Lyme disease can be cured with oral antibiotics if it is caught early. If diagnosed at a later phase in the disease, patients may need intravenous antibiotics in hospital.

Putting to work his 25 years of experience as a DNA and protein biochemist, Heritage Scientist Dr. George Chaconas is studying the *Borrelia burgdorferi* organism that causes Lyme disease, with a view to developing drugs that can either block or treat infection. "If we don't understand how this organism works, then there's not a lot we can do to combat it," explains Dr. Chaconas. "It's like an automobile–if you don't know how it works you can't fix it when it breaks. We have the potential to find a very specific drug that treats only Lyme disease, and that may allow elimination of *Borrelia burgdorferi* infection from the animal reservoir."

Lyme disease can affect the joints, the nervous system, the heart, and the skin.

Basic research is important, even though it may be a step or two removed from treatment in the clinic, stresses Dr. Chaconas, a professor at the University of Calgary. Together with members of his lab, he investigates the unusual way in which bacteria that cause Lyme disease carry their DNA or genetic material. While most bacteria have a single circular chromosome, the genetic material in *Borrelia* is unique. *Borrelia* is spiral-shaped (a "spirochete"). The genome is segmented and made up of more than 20 separate pieces of DNA. What's more, most of these DNA segments have a linear rather than a circular shape, and hairpin-like ends called "telomeres". Dr. Chaconas' team studies *Borrelia's* unusual genome structure, the mechanism by which the DNA is copied and faithfully passed on from generation to generation, and *Borrelia* cell division. They also explore how this organism adapts itself to be able to live in a mammalian host without being killed by the mammal's immune system.



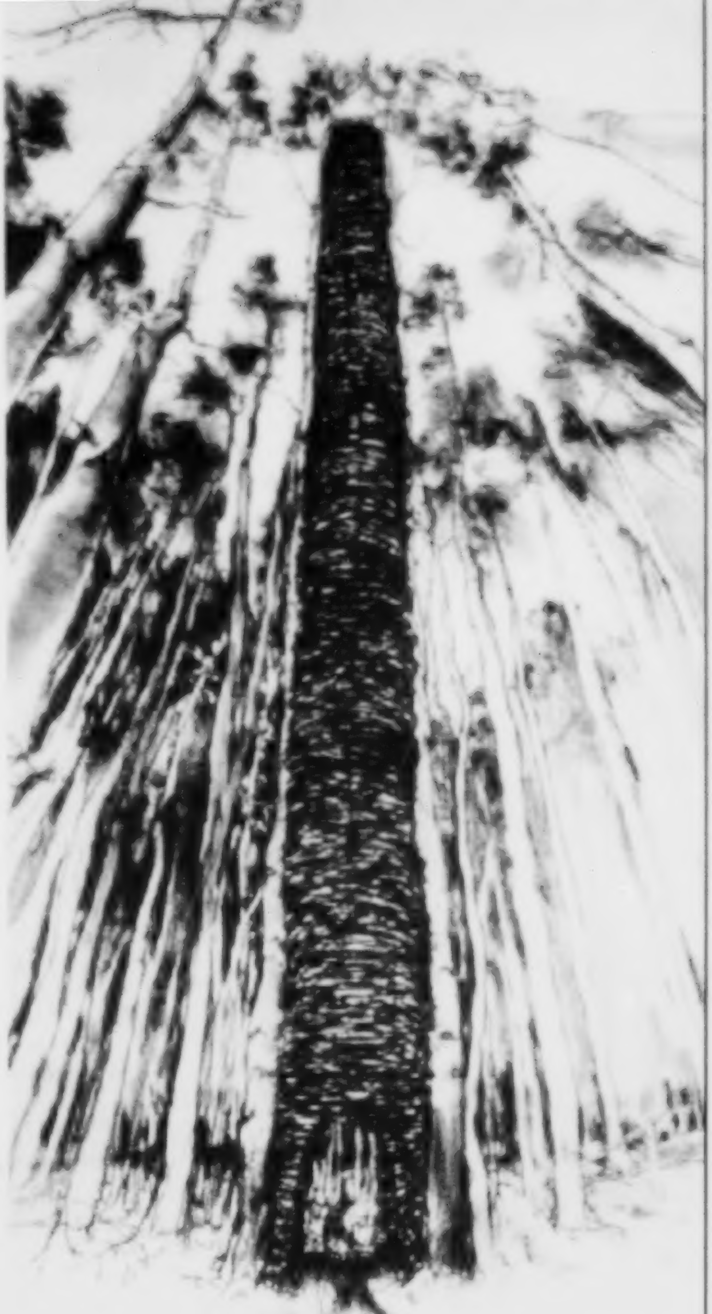
DR. GEORGE CHACONAS

"This organism has a genome unlike any other bacteria."

"What interests me is that this organism is in many ways very exotic," he explains. "It has a genome unlike any other bacteria. We're gaining an understanding of a unique enzyme and how it works to copy the unusual DNA with hairpin ends. This enzyme provides us with a unique target for drug development."

Dr. Chaconas moved to Calgary from London, Ontario, a year and a half ago so he could join the university's Bacterial Pathogenesis Research Group and research Lyme disease. "Without Heritage funding it would have been impossible for me to move my laboratory here and to set it up very quickly with all the equipment that we needed," he says.

Dr. George Chaconas is a Heritage Scientist and a professor in the Department of Biochemistry & Molecular Biology and the Department of Microbiology & Infectious Diseases at the University of Calgary, where he chairs the Bacterial Pathogenesis Research Group. He is a Canada Research Chair in the Molecular Biology of Lyme Disease, and the recipient of a John Simon Guggenheim Fellowship; the Roche



Diagnostics Award for Biomolecular and Cellular Research; a CIHR Distinguished Scientist Award; and the Canadian Biochemical Society Pharmacia Award.

Selected publications

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Kobryn K, Chaconas G. ResT, a telomere resolvase encoded by the Lyme disease spirochete. *Molecular Cell* 2002 Jan;9(1):195-201.

ARTWORK: PETER VON TIESENHAUSEN, TOWER, CHARCOAL, CONTE, CHALK, GRAPHITE ON PAPER, 198.5 X 107 CM, 1993. COURTESY OF THE ALBERTA FOUNDATION FOR THE ARTS.

Lyme disease

For many years, Lyme disease was confused with other disorders, such as rheumatoid arthritis. It was first identified in 1975 in Old Lyme, Connecticut, when researchers found that 51 individuals in a small geographical area had developed the same symptoms at the same time of year.

Transmitted by infected ticks, Lyme disease affects both men and women, of any age. Most cases can be cured with antibiotics if treated early. A severe rash with a pattern like a bull's eye or a ring-within-a-ring appears at the site of the tick bite in 70% of cases. Other symptoms include fatigue, headaches, fever, chills, aching joints and muscles, and skin sores or rashes. If not treated, Lyme disease can ultimately affect joints, the nervous system, and the heart.

Lyme disease is prevalent in Europe, the former Soviet Union, China, Japan, and Australia. In North America it is most common in the northeast and north-central regions, and less common on the West Coast. The exact number of Canadians affected by Lyme disease is not known, but Long Point and Point Pelee in Ontario are "hot spots" for the disease.

Borrelia has been found in rabbit ticks in the fields of Alberta, which means that the bacteria causing Lyme disease are in our province. However, the tick that might transmit this bacteria from the hare to humans hasn't been found here—not yet, at least. It seems the tick cannot survive in Alberta's dry climate.

However, if you wish to protect yourself against Lyme disease in wooded areas or tall grass in areas where the disease is known to exist, you should wear both protective light-coloured clothing (long-sleeved shirts, tucked into pants) and insect repellent with the active ingredient DEET. You should carefully check for and remove any ticks, which can be as small as a millimetre in length.

S T R

stroke is a sudden loss of brain function caused by the interruption of blood flow to the brain, either due to ischemia (blood-vessel blockage) or hemorrhage (blood-vessel rupture). It is the fourth biggest killer and the leading cause of disability in Canada. Stroke survivors can suffer devastating and disabling effects ranging from paralysis, speech difficulties, memory loss, and even behavioural changes.

People who live to the age of 80 have a one-in-four chance of experiencing a stroke. And sadly, given Canada's aging population, most of us will have to cope with stroke at some point in our lives—whether it hits us personally, or a member of our immediate family or our spouse's family.

In Canada, the mortality rate from stroke is approximately 20%, but stroke research and patient care in Alberta have already made a difference. In Calgary the rate is down to about 10%. Stroke patients in the city spend less than 4 hours in the emergency ward as opposed to the 20 to 30 hours that used to be the norm. Significantly, this saves the health system about 45 beds, which would cost an extra $50 million each year.

fighting the devastation

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The Calgary Stroke Program

The main reason for this success is the Calgary Stroke Program, directed by AHFMR Scientist Dr. Alastair Buchan. Built over the past eight years and staffed at present by a team of 50 people, this program provides acute, rehabilitative, and preventive care to stroke patients in a unique continuum spanning the range from experimental to clinical work. The program is conducting three research projects: One project looks at patients who have suffered an acute stroke to determine who recovers well and who doesn't; another examines susceptibility to stroke based on risk factors and on previous experience of a ministroke; and the third studies how stroke patients recover.

"Every stroke is different," says Dr. Buchan. "Some people have a stroke and recover; others are left devastated. These differences can be explained to some extent by the patient's age, by the severity of the stroke, or by other risk factors such as diabetes or high blood pressure, but a lot of the variance is not explained. We want to know why these differences exist."

"Every stroke is different."

Dr. Buchan explains that those who have tissue damage from a ministroke–a transient ischemic attack–are probably more sensitive and more likely to have further stroke events. Those without tissue damage are more resistant. "We're trying to determine if there are different gene

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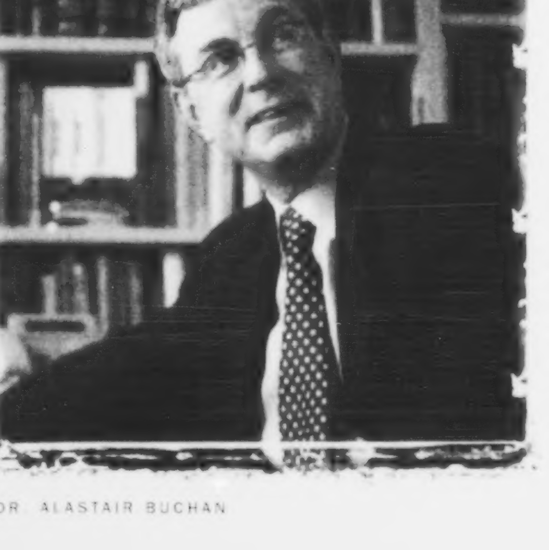

DR. ALASTAIR BUCHAN

STROKE

patterns in those who are more susceptible to stroke versus those who are more tolerant."

One of the program's projects is a study called FASTER (Fast Assessment of Stroke and TIA to prevent Early Recurrent Events). Patients who suffer these TIAs are at high risk for a full-blown stroke. Whereas most stroke studies take 3 to 6 months to put TIA patients into a randomized trial—FASTER takes 3 to 6 hours. Getting this high-risk population into treatment immediately could dramatically reduce their chances of suffering a major stroke.

The Seaman Centre

Key to the Calgary Stroke Program's unique ability to see stroke patients quickly are the scientists at the Seaman Family MR Research Centre at the Foothills Hospital. Using magnetic resonance imaging (MRI), researchers and clinicians are able to identify the TIA patients with a higher risk of experiencing a full stroke, and then treat those patients to prevent it.

AHFMR Clinical Investigator Dr. Andrew Demchuk is a stroke neurologist who examines stroke patients using MRI, CT, and ultrasound techniques. He then tracks these patients for two years, in hopes of identifying features that will determine which ones are at high risk for a recurrence or a more serious incident. "We've done everything we can to set up an environment in which someone who has a stroke within a hundred miles of the Foothills Hospital gets in to us very quickly," says Dr. Demchuk. "We have a team that deals with these patients very quickly and we do our imaging very quickly. It's a unique set-up and it allows us to provide a very high level of care. It's the reason I'm in Calgary."

Dr. Demchuk applies MRI techniques and makes them work for patients.

While Dr. Demchuk applies MRI techniques and makes them work for patients, AHFMR Scholar Dr. Richard Frayne is the MRI physicist who develops the techniques. Dr. Frayne also came to Calgary because of the opportunity offered by the Seaman MR Centre, arriving the same week the huge magnet became operational. He uses it in his study of blood flow, to take pictures of the shape of blood vessels to find blockages.

LEFT TO RIGHT: DRS. RICHARD FRAYNE, ROSS MITCHELL, AND ANDREW DEMCHUCK

Moving to a tissue window

Time is truly of the essence when it comes to stroke. The only treatment currently available for stroke patients is a clot-busting drug called tPA (tissue plasminogen activator), which can dissolve blockages causing stroke or heart attack. However, tPA has strict limitations, making only a fraction of patients eligible—it is only approved for patients within the first three hours of their stroke. After that time window, patients do not seem to benefit.

"We're trying to move from a time window to a tissue window for treatment," explains Dr. Frayne. "Using a combination of medical imaging techniques, we want to determine which patients would benefit from receiving tPA, even outside that three-hour window. We want to tailor the treatment to the individual."

Time is truly of the essence when it comes to stroke.

Dr. Frayne is also interested in using MR imaging for stroke prevention, to assess which patients are at greatest risk by looking at the blood vessels in the neck to spot regions that are partially blocked. He also studies new ways of treating stroke that involve MR imaging to assess the therapy and monitor the re-establishment of blood flow. "Someday this magnet could be used for stroke prevention, treatment, and follow-up," he says.

Another cog in the wheel at the Seaman Centre is AHFMR Scholar Dr. Ross Mitchell. Dr. Mitchell does biomedical informatics—he uses mathematics and computers to analyze the MR imaging and to find better ways of producing those images. "We're applying information technology techniques from fields like geophysics and astronomy, and applying them to solve medical problems," he explains.

A unique group

Dr. Mitchell attributes much of the Centre's success to the unique interdisciplinary group of researchers situated right in the hospital instead of in a separate department on the main campus. He encourages his students and post-docs to attend stroke rounds every week, in order to listen to clinical discussion about how to treat patients. "My rule of thumb is to be no more than 50 metres from where the patients are treated—that's how we get a lot of our ideas for research." He

Dr. Mitchell attributes much of the Centre's success to the unique interdisciplinary group.

The evolution of blood-vessel imaging with MRI

The blood vessels feeding the brain are often imaged to assess potential risk for stroke. Ten years ago an invasive diagnostic x-ray angiogram was the most common approach for imaging these vessels. Today, thanks in part to an Edmonton scientist, a safer and less expensive procedure using magnetic resonance imaging (MRI) has become more widespread.

AHFMR Senior Scholar Dr. Alan Wilman is an MRI physicist who designs and applies new magnetic resonance techniques for blood-vessel imaging. MRI is a non-invasive way of taking pictures of tissues and organs that uses powerful magnets. "MRI is not like an x-ray—it's not a simple technique," says Dr. Wilman. "It involves a lot of variations in magnetic fields and a lot of physics. It's also very new. MR angiography was developed in 1985 and is really just reaching its adulthood, while x-ray angiography has been around since 1896. So MRI still has a lot of potential to evolve."

Dr. Wilman's technique was actually an improvement on an existing method called contrast-enhanced MR angiography, first introduced in 1994. Dr. Wilman figured out how to make this technique work better by maximizing the image contrast and finding a new way to acquire the data. It has now become a standard technique and is used worldwide on more than 600,000 patients a year.

Dr. Wilman conducts his work at the University of Alberta's NMR Centre in the basement of the hospital's emergency wing. The facility has a standard 1.5-tesla strength MRI, as well as double- and triple-strength magnets (3 and 4.7 tesla respectively). Triple strength is the highest field in Canada for human imaging.

"Double-strength MRI has become the clinical standard in the time that I've been here. But when I first started, people didn't think research with double strength was relevant because it wasn't the strength that was used clinically," explains Dr. Wilman. "Since the birth of MRI there has always been a progression to higher and higher fields, which give better image quality. So I'm now involved in designing new techniques for these higher fields, as well as in refining some of the MRI techniques used in the clinic."

Dr. Alan Wilman is an AHFMR Senior Scholar and associate professor in the Department of Biomedical Engineering at the University of Alberta. He also receives funding from the CIHR and the Whittaker Foundation.

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Wilman AH, Riederer SJ, Huston JH, Wald JT, Debbins JP. Arterial phase carotid and vertebral artery imaging in 3D contrast-enhanced MR angiography by combining fluoroscopic triggering with an elliptical centric acquisition order. *Magnetic Resonance in Medicine* 1998 Jan;40(1):24-35.

Al-Kwifi O, Emery DJ, Wilman AH. Vessel contrast at three Tesla in time-of-flight magnetic resonance angiography of the intracranial and carotid arteries. *Magnetic Resonance Imaging* 2002 Feb;20(2):181-187.

ABOVE: DR. ALAN WILMAN

The dangers of the ministroke

For years studies have suggested that patients who experience a ministroke (TIA) have a high risk—approximately 10%—of experiencing a full-blown stroke in the following 90 days, and especially during the first week afterward. Using 10 years of patient data from a large multicentre clinical trial, AHFMR Senior Health Scholar and biostatistician Dr. Michael Eliasziw has recently added to this picture.

Dr. Eliasziw analyzed data from patients who had experienced a TIA and had atherosclerosis (hardening of the arteries) in the carotid artery (the main artery in the neck). "We found that these people had a 20% risk of stroke within the next 90 days after a TIA," says Dr. Eliasziw. He adds that patients coming to the emergency room with a TIA should have ultrasound, MRI, or x-ray angiography, to allow doctors to examine blood vessels in their necks for atherosclerosis. "These imaging procedures would allow differentiation of those patients at even higher risk of stroke."

The analyses also showed that while people with atherosclerotic disease have a higher risk of stroke, the amount of plaque has nothing to do with the short-term prognosis. It had often been assumed that the more plaque in the artery, the more likely that it would break off and cause an interruption of blood flow to the brain. In reality, it appears that the amount of plaque at the time of the TIA has nothing to do with whether the patient will have a stroke. "It is whether you have plaque and its level of stability that matters, not how much," explains Dr. Eliasziw.

Dr. Michael Eliasziw is an AHFMR Senior Health Scholar and an associate professor in the University of Calgary Department of Community Health Sciences. He also receives funding from the Natural Sciences and Engineering Research Council of Canada (NSERC).

Selected publication

Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJM, for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. *Canadian Medical Association Journal* 2004 Mar 30;170(7):1105-1109.

ABOVE DR. MICHAEL ELIASZIW

explains that one project got its start on the way back from stroke rounds because of a discussion between a stroke neurologist, a physicist, a computer scientist, and an electrical engineer about the patient they had just seen. "I don't know of many places in Canada that have that kind of connection."

Dr. Mitchell and his colleagues are building a computer model based on MR imaging to predict which brain tissue will live and which will die in stroke patients. Patients come back to be scanned 30 days later, and the prediction can be checked. "This kind of computer image would allow doctors to treat based on the patient's individual physiology and not just based on that three-hour time frame," he says. "It could revolutionize stroke treatment."

MRI techniques

Edmonton also has a first-rate MRI set-up right next to an emergency ward in the University of Alberta NMR Centre. The facility allows scientists to study stroke using three MRI magnets dedicated solely to research. AHFMR Scholar Dr. Christian Beaulieu works in the Centre, developing new MRI techniques to evaluate and monitor brain injury after stroke.

DR. CHRISTIAN BEAULIEU

"We're interested in how the wiring changes after a stroke."

One of Dr. Beaulieu's projects deals with non-invasive measurements of blood flow in the brain. The standard method of measurement involves the injection of a contrast agent which is then observed as it passes through the brain to get an idea of the blood flow. New techniques can measure blood flow without the contrast agent by using magnetic resonance to tag blood in the neck and watch where it goes in the brain–a less expensive method, which also allows the scan to be repeated. "We're trying to optimize this method for the elderly population, the population most at risk for stroke," says Dr. Beaulieu, explaining that the elderly tend to have slower blood flow in the brain. "We will then compare this method to that of the contrast agent, and see if it works as well to detect the areas of low blood flow in the brain that are causing the stroke."

Another project examines white-matter degradation after a stroke. White matter can be thought of as the wiring that allows different parts of the brain to communicate with one another. "We're interested in how the wiring changes after a stroke," says Dr. Beaulieu. "How it degrades over time–how much and how fast.

"These and the other techniques we're working on are all geared toward a better understanding of what is happening early on in acute stroke," he continues. "The power of MRI is in its ability to take different types of pictures that give you critical information that otherwise would be unattainable with alternative imaging methods like x-ray and CT."

Hypothermia

While MRI is undoubtedly a wonderfully diverse tool for stroke research, it is not the only means by which Heritage researchers in Alberta are tackling the disease. In a non-clinical research setting, Dr. Fred Colbourne looks for ways to reduce injury and promote recovery after a stroke. One of his primary interests is the study of how hypothermia can reduce cell and brain damage in stroke victims–an area he has been working in for over a decade. Scientists have known for many years that cooling can reduce the injury that an organ suffers. Recent cases like Baby Erika, the Edmonton toddler who survived several hours in sub-zero temperatures, have illustrated the effectiveness of cooling in preserving tissue. Dr. Colbourne explains that since cooling patients too much causes cardiac complications, his approach is to use a much milder level of hypothermia–33°C (normal body temperature is around 37°C).

DR. FRED COLBOURNE

"We've studied this in a number of different stroke models and have learned that hypothermia can reduce injury if you prolong it. With a short period of hypothermia–a couple of hours or even half a day–the amount of protection is trivial. It may reduce cell death, but not permanently."

"Hypothermia can reduce cell death."

The hippocampus (the part of the brain responsible for memory) is particularly sensitive to stroke. Because these cells don't die immediately after the event but over a period of several days, the time between when the stroke occurs and when cell death occurs is an opportunity. "Hypothermia can reduce cell death if you intervene early enough within a window of about twelve hours," says Dr. Colbourne, pointing out that there is only a three-hour window in which to use clot-

busting drugs for stroke patients.

Dr. Colbourne also studies the effect of hypothermia on hemorrhagic stroke (when a blood vessel in the brain actually ruptures). Initially Dr. Colbourne thought that hypothermia did nothing for this type of stroke—until he realized he was trying it too early. "Intervening too early after a hemorrhagic stroke seems either to make matters worse or else brings no benefit," he explains. "This is because there are some side effects to hypothermia. It is known to prolong bleeding time, for example, which isn't a problem in uncomplicated ischemic stroke models, but aggravates bleeding in hemorrhagic stroke. Now our focus is on how to treat these side effects so we can intervene earlier."

Dr. Kleim wants to understand how the brain recovers after stroke.

Recovery

AHFMR Senior Scholar Dr. Jeffrey Kleim is also interested in promoting recovery after stroke, but rather than focusing on trying to save the brain tissue that has been damaged, he focuses on the tissue that remains. He wants to understand how the brain recovers after stroke and use that information to guide the development of therapies for the clinic.

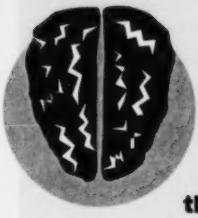
Patients undergo motor rehabilitation to help them recover from movement difficulties induced by stroke. Some people show good recovery rates, but others do not. Dr. Kleim wants to know what happens in the brains of patients who recover. "We want to figure out how the brain adapts to the fact that it's missing a piece of tissue," he says. "If we can understand the mechanisms, we might be able to come up with interventions that promote that process. So we're doing experiments with drugs that might promote the recovery process, and we're also trying to figure out the best kind of therapy to give and the best time to give it."

The theory is that if you lose one part of your brain, other parts of the brain take over. For this to happen, some neurobiological change has to occur in those areas. Dr. Kleim uses a technique that allows him to map movement in the brain. He explains that different regions of the brain control different body parts. "The part that controls your wrist is right next to the part that controls your fingers so the brain is actually a map of your body. We make what are called motor maps, where we take a picture of the top of the brain—almost like an aerial photograph—then pass small amounts of current through different areas to see what movements are produced."

After rehabilitation, the brain can be mapped again to see how the map has changed in response to both the damage and the therapy. The area which may have controlled your elbow before a stroke might now control your fingers, to compensate for lost tissue. "It's quite remarkable that the brain has the capacity to do this and can adapt so quickly," says Dr. Kleim. "We want to know what happens to the neurons within these brain areas that are undergoing change, and what it is about physical therapy that drives these changes."

"There is some very exciting stroke research going on in Alberta," summarizes Dr. Alastair Buchan.

DR. JEFFREY KLEIM



Symptoms of TIA and stroke

Call 911 immediately if you experience one or more of the following symptoms:

- Sudden loss of speech or the ability to understand speech
- Sudden weakness, numbness or tingling paralysis in the face, arm or leg
- Sudden severe or unusual headache
- Sudden loss of vision in one eye or toward one side
- Sudden loss of balance or co-ordination

Source: Heart and Stroke Foundation of Canada

"But prevention is also key. It's so important for people to choose a healthy diet and get regular exercise. We need to move beyond simply coping with this devastating illness after it happens."

Dr. Alastair Buchan is a full professor in the University of Calgary Department of Clinical Neurosciences, and director of the Calgary Stroke Program. He is an AHFMR Scientist and also receives funding from the Heart and Stroke Foundation (both provincially and nationally), the Canadian Stroke Network, the Canadian Institutes of Health Research (CIHR), the Canada Foundation for Innovation (CFI), and Western Economic Diversification Canada.

Dr. Andrew Demchuk is an AHFMR Clinical Investigator and assistant professor in the University of Calgary Department of Clinical Neurosciences. He also receives funding from the Heart and Stroke Foundation of Canada, CIHR, and the National Institutes of Health (NIH) in the United States.

Dr. Richard Frayne is an AHFMR Scholar and an associate professor in the departments of Radiology and Clinical Neurosciences at the University of Calgary. He also receives funding from the Heart and Stroke Foundation of Canada and the Canada Research Chair program.

Dr. Ross Mitchell is an AHFMR Scholar and associate professor in the departments of Radiology and Clinical Neurosciences at the University of Calgary. He also receives funding from CIHR, the MS Society of Canada, and the Heart and Stroke Foundation of Canada.

Dr. Christian Beaulieu is an AHFMR Scholar and assistant professor in the Department of Biomedical Engineering at the University of Alberta. He also receives funding from CIHR, the Heart and Stroke Foundation of Canada, NSERC (Natural Sciences and Engineering Research Council of Canada), and the Whittaker Foundation.

Dr. Frederick Colbourne is an AHFMR Scholar and an associate professor in the University of Alberta Department of Psychology. He also receives funding from the Canadian Stroke Network, CIHR, NSERC, and the Heart and Stroke Foundation of Canada.

Dr. Jeffrey Kleim is an AHFMR Senior Scholar and an associate professor in the University of Lethbridge's Department of Psychology and Neuroscience. He also receives funding from CIHR, NSERC, the Canadian Stroke Network, and the NIH.

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Commercializing THE WalkAide

An innovative medical device, developed in Alberta with the help of funding from AHFMR, has been licensed to the US-based Hanger Orthopedic Group, Inc., one of the world's largest providers of orthotic and prosthetic patient-care services.

The technology treats foot drop–a condition where a stroke or spinal-cord injury causes the patient to drag a foot while walking. The device restores control of the foot by using electrical stimulation to recreate a natural nerve-to-muscle response. It was invented and developed by University of Alberta neuroscience professor Dr. Richard Stein and his company, BioMotion Ltd.

The licensing agreement between BioMotion and Hanger Orthopedic Group is a landmark for both companies. For Hanger, it represents the company's first step into the development and commercialization of a new line of neuromuscular devices. For BioMotion, the agreement represents a major breakthrough in its efforts to see the technology gain widespread use.

The device restores control of the foot.

Dr. Stein has been working on the device, dubbed "WalkAide", since 1994. He formed BioMotion to commercialize WalkAide and other technologies coming from his research. Funding from AHFMR's Technology Commercialization (TC) Program took WalkAide from prototype through to clinical trials. However, substantially more funds were needed to move the product to market, especially to ensure that WalkAide would meet the requirements of regulatory agencies, which oversee the use of such devices, and insurers (such as Medicare in the United States), which pay for them.

"Patients see an immediate and substantial benefit."

The situation appeared to improve when a new company, NeuroMotion Inc., was set up in 1996 to commercialize Canadian neuroscience devices. NeuroMotion licensed the WalkAide technology and others but failed to raise sufficient venture capital to advance products to commercial launch. The company ceased operations in 2000.

Although the NeuroMotion experience was extremely disheartening, it did not diminish Dr. Stein's resolve to see patients benefit from his invention. "Maybe I'm just stubborn, but I wasn't going to give up on this," he says. BioMotion reacquired the rights to its technology and started once again on the road to commercialization.

Money, however, was still an issue. In a highly unusual move, the TC Program agreed to refund the WalkAide project. The goals were to develop a business plan, construct prototypes and undertake clinical trials of a second-generation WalkAide model. BioMotion was also referred to ForeFront, a relatively new addition to the TC Program.

ForeFront takes an integrated approach–helping innovators and their teams understand critical business issues and processes through interaction with a group of technology, business, market, and entrepreneurial experts. This process provides valuable knowledge and experience in such areas as intellectual property, product testing, scale-up, marketing, and business planning and strategies. Rick Brommeland, an Edmonton-based management and technology consultant, was assigned to work with BioMotion.

"To be honest, I didn't think ForeFront was going to be much help," says Dr. Stein. "I thought we were going to get yet another consultant who just wanted to do a business plan. As it turned out, Rick came in and seized the situation. He went through the issues we were facing and developed an action plan."

The plan involved contacting companies that might be interested in buying or licensing the WalkAide technology. Rick Brommeland followed up on the contact list and arranged a number of meetings between BioMotion and interested parties. Hanger Orthopedic Group was on that list.

"What caught our eye about the BioMotion technology was the reaction from patients," says Jeff Martin, vice-president of Product Marketing at Hanger. "People don't want to take it off. They see an immediate and substantial benefit.

"The professionals are equally excited about the technology. As part of our due diligence, we flew senior clinicians from all over the US to Vancouver to observe and talk to patients using WalkAide. Their reaction was very positive."

In May 2004 Hanger announced the licensing agreement with BioMotion and the formation of a wholly owned subsidiary, Innovative Neurotronics, Inc. (IN, Inc.). This new company will specialize in the development and commercialization of devices that use electrical stimulation to improve the

DR. RICHARD STEIN

THE WalkAide

functionality of an impaired limb. The term Myo-Orthotics technology has been coined by IN, Inc. for its initial product line. It represents the merging of orthotic technology, which braces a limb, with electrical stimulation, which restores actual function.

The hoopla over the agreement is somewhat bittersweet for Dr. Stein, who remains involved with WalkAide development as a consultant to IN, Inc. "My ultimate dream would have been for BioMotion to do this on its own," he says. "We really did try, but we didn't have the funding or the expertise that Hanger does in regulatory issues, product design, and dealing with insurers. As well, Hanger's market reach—the company has more than 600 patient-care centres in the US—is beyond our grasp.

"This agreement will bring substantial royalties to Alberta and the chance for more products in our research labs to be commercialized. And personally, as a scientist, what I really want is to see the things I've done help people. This is truly our best opportunity."

This sentiment is echoed by Hanger's Jeff Martin. "We have an opportunity to benefit thousands and thousands of patients who are recovering from debilitating conditions such as spinal-cord injury, stroke, Parkinson's disease, and more. They struggle every day, and this is a product that offers the potential for greater mobility, functionality, and patient freedom."

Dr. Richard Stein is a full professor in the Department of Physiology and a member of the Centre for Neuroscience at the University of Alberta. In addition to TC funding from AHFMR, he receives support from the Canadian Institutes of Health Research, the Canada Foundation for Innovation, the Alberta Science and Research Investments Program, and the Christopher Reeve Paralysis Foundation.

Hanger Orthopedic Group, Inc. (NYSE:HGR), headquartered in Bethesda, Maryland, provides orthotic and prosthetic patient-care services. Hanger is the market leader in the United States, owning and operating more than 600 patient-care centres in 44 states and the District of Columbia, and has approximately 3,200 employees.

When it comes to kidney failure, 29-year-old Sean Molofee has had more experience than anyone would ever want. The St. Albert native's battle with kidney disease began in his teenage years and led to a kidney transplant at age 26. Unfortunately he lost the transplant, due to complications, after just 36 hours.

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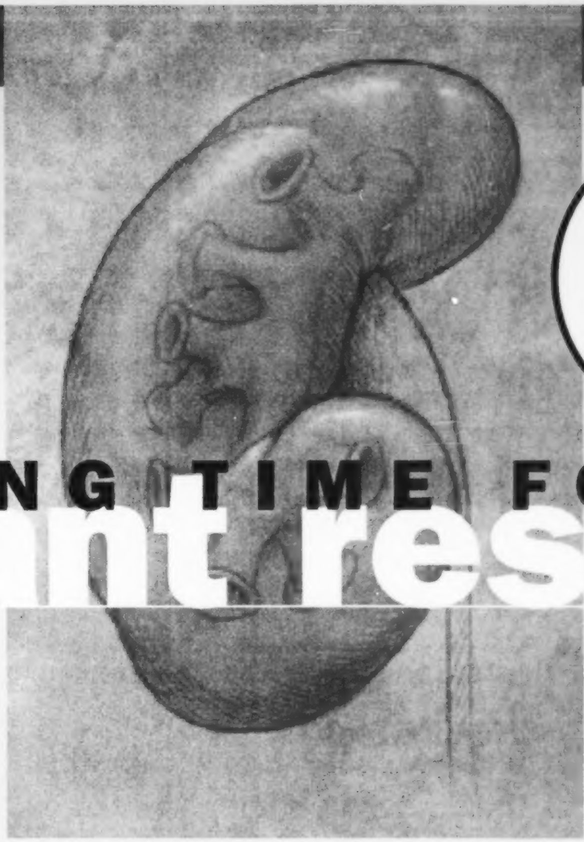
Molofee then went on dialysis, a life-saving procedure that mimics some of the blood-cleaning functions of the kidneys. Dialysis kept him alive but the procedure, which could take up to six hours and was repeated three times a week, amounted to what Molofee describes as "three and a half years of hell". The nightmare came to an end on January 29 of this year, when he received a new kidney from a deceased donor. "The successful transplant represents the opening of every door that closed on me when I first found out I had kidney failure," Sean says, "a return to the life I once had."

Dialysis amounted to "three and a half years of hell".

Molofee's situation is not unusual. Approximately 25,000 Canadians live with kidney failure. Each day, 10 Canadians learn that their kidneys have failed and that their survival depends on dialysis or a kidney transplant. At the end of 2001, 3,500 Canadians were on a waiting list for an organ transplant, and 80% of those were waiting for a kidney.

"The short-term outcomes for kidney transplants have improved considerably," says AHFMR Clinical Investigator Dr. Sita Gourishankar, a kidney-trans-

ABOVE: DR. SITA GOURISHANKAR AND SEAN MOLOFEE



"The short-term outcomes for kidney transplants have improved considerably."

"If there's one thing I'd throw myself behind, it's transplantation research," says Molofee, who is now looking forward to a future that will include training as a massage therapist. "Anything to help people get free from the dialysis

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ant research

machines has my full support. And for those with transplants, it would be great to see rejection become a problem of the past. To lose what I now have would be a crippling blow, both mentally and physically."

plant researcher at the University of Alberta and a practising physician. "But in the longer term, we still have transplants that fail over time, resulting in patients' returning to dialysis, or dying. That's why research in this area is so vital."

AHFMR Senior Scholar Dr. Ron Moore agrees. Dr. Moore, Sean's transplant surgeon, is also a U of A researcher who studies bladder and prostate cancers. In addition he and co-workers are investigating strategies to prolong the life of transplanted organs.

Dr. Gourishankar and Dr. Moore are among the 40 researchers across the province who have been offered a total of $22 million in funding this year by the Alberta Heritage Foundation for Medical Research. With AHFMR support, Dr. Gourishankar will probe the mysteries of kidney-transplant failure. This is an exciting time for transplant research because scientists now have detailed genetic information about the inflammatory processes behind rejection. The answers may lead not only to new ways to prevent transplant rejection and failure, but also to new treatments for kidney disease and other diseases involving the immune system.

Dr. Sita Gourishankar is an AHFMR Clinical Investigator and an assistant professor in the Division of Nephrology and Transplantation Immunology, in the Faculty of Medicine at the University of Alberta. She also receives funding from Genome Canada, the University Hospital Foundation, and Amgen Canada Inc.

Dr. Ron Moore is an AHFMR Senior Scholar and professor in the University of Alberta Department of Surgery, Faculty of Medicine. He receives additional funding from the Kidney Foundation of Canada, the National Cancer Institute of Canada, and the Alberta Cancer Board.

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RIGHT: DR. RON MOORE

A stress test for stroke

Ashley Harris is a Heritage Student working with senior researchers at the Seaman Family MR Research Centre in Calgary, where she is helping to investigate vascular disease and other medical problems.

Ashley, a biological engineer, hopes to develop a test that can predict if a patient is likely to have a stroke, and if so, how severe that stroke may be. The idea is to try to lessen the impact of stroke through improved prevention, detection, and rehabilitation. If successful, this research could have major implications for individuals susceptible to stroke.

If your doctor is worried that you may be at high risk for coronary artery disease or a heart attack, you may be sent for a cardiac stress test to assess how your heart and vascular system respond to stress during exercise. During a stress test you will be asked to walk on a treadmill or pedal on a stationary bicycle while your blood pressure and heart function are monitored. The results of this test predict the likelihood of your having a heart attack.

Ashley hopes to develop a stroke stress test that will work in a similar way to predict the risk of a stroke. At present, it's difficult to predict whether someone with heart disease is more likely to have a stroke than a heart attack.

"The risk factors for a stroke are pretty similar to the risk factors for a heart attack," explains Ashley. "They're pretty much the same thing. With a stroke, a blood clot occurs in an artery of the brain. With a heart attack, the clot is in an artery of the heart."

Normally, when the brain does not receive sufficient oxygen (hypoxia) and/or there is too much carbon dioxide (hypercapnia), cerebral blood flow is increased to maintain oxygen levels and remove excess carbon dioxide. Those who are more suscepti-

RIGHT: ASHLEY HARRIS

"The risk factors for a stroke are pretty similar to the risk factors for a heart attack."

ble to stroke may have less of a response to these conditions, or a delayed response. Combining her biomedical and engineering training, Ashley investigates how MRI (magnetic resonance imaging) might measure the brain's response to the flow of oxygen and carbon dioxide in blood to and from the brain. She is also working on a project to understand and reduce natural cerebral blood flow variability, which is probably the dominant source of noise (i.e., unclear signals or disturbances) in these MR imaging techniques.

"I'm excited about this," she says. "Though this work is in its infancy–I have more questions than I do answers right now–there's a possibility this research may also help improve the quality of MRIs for all patients, not just for stroke patients."

Ashley also investigates "collateral circulation". When a patient has a stroke, a blockage in an artery in the brain prevents the brain cells from receiving adequate blood supply. Yet in some individuals–those with "collateral circulation"–other arteries in the brain compensate so efficiently that less brain damage occurs, and sometimes none at all.

AHFMR Student Ashley Harris is pursuing a master's degree in electrical engineering (with a biomedical specialty) under the supervision of AHFMR Scholars Dr. Richard Frayne and Dr. Marc Poulin. She receives additional funding from NSERC and iCORE. While studying for her undergraduate degrees in engineering and biology, Ashley spent two summers as a Heritage Summer Student.

reader resources

Regulating calcium

University of Calgary Smooth Muscle Research Group
http://www.ucalgary.ca/smrg/

Cell communication

Dr. Rick Wozniak's web site
http://www.ualberta.ca/~anatomy/cellbiol/wozniak.html

Will you be safe in the woods today?

University of Calgary Bacterial Pathogenesis Research Group
http://www.med.ucalgary.ca/webs/bprg/

Fighting the devastation of stroke

Heart and Stroke Foundation of Canada
http://www.heartandstroke.ca

Calgary Stroke Program
http://www.crha-health.ab.ca/stroke/CSPWebPages/

Canadian Stroke Network
http://www.canadianstrokenetwork.ca

Seaman Family MR Research Centre
http://www.med.ucalgary.ca/mrcentre/

Stroke Survivors Canada
http://www.strokesurvivors.ca

University of Alberta In Vivo NMR Centre
http://www.invivonmr.ualberta.ca/

Commercializing the WalkAide

Hanger Orthopedic Group Inc.
http://www.hanger.com

AHFMR's Technology Commercialization Program
http://www.ahfmr.ab.ca/tc/

An exciting time for transplant research

Dr. Sita Gourishankar's web site
http://www.departmentofmedicine.ualberta.ca/research/researcher_gourishankar.htm

Dr. Ron Moore's web site
http://www.ualberta.ca/~oncology/faculty/moore/

Heritage Youth Researcher Summer (HYRS) Program 2004

Sarah Fung is one happy young lady. After working very hard at school she has been rewarded with an exceptional opportunity—she will spend six weeks this summer learning about life as a scientist and health researcher while performing hands-on biomedical research in the lab of a researcher at the University of Calgary.

Sarah is a Grade 11 student in the International Baccalaureate Diploma Programme at Western Canada High School in Calgary. She was one of 206 applicants this year from 72 schools throughout Alberta competing for a place in the AHFMR-funded Heritage Youth Researcher Summer (HYRS) Program. Sarah was one of 45 exceptional students selected from 42 schools around the province to attend the University of Calgary, the University of Alberta, or the University of Lethbridge in the 2004 HYRS Program. To qualify for this program, students who love science must have an 85% average in the required math and science subjects, obtain two teacher references and a community reference, and write an essay on an assigned topic.

ABOVE: SARAH FUNG AND DR. JEFFREY GAUDET

Applications for the HYRS Program are judged by a committee of three teachers.

"I'm really looking forward to being part of the program," says an excited Sarah. "I'm interested in the medical field and I thought this would be a good opportunity to get some experience."

Sarah will work under the supervision and mentorship of Heritage Scholar Dr. Jeffrey Gaudet, an assistant professor in the Department of Biochemistry and Molecular Biology in the Faculty of Medicine. Dr. Gaudet, a member of the Genes and Research Development Group at the U of C, investigates how genes control the formation of organs. He studies the development of a simple organ–the pharynx–in a little worm (about 1 millimetre long) known as *Caenorhabditis elegans*. The goal is to understand how cells are instructed to form an organ. In the lab, Sarah will look for new mutations that affect formation of the pharynx, in order to better understand the normal process of organ formation.

"I'm really glad to be a part of the program," says Dr. Gaudet. "I think it's a great opportunity for high-school students to get a sense of what research is really like and of the different career opportunities."

"Genetics is interesting because it really holds the key to what humans are like," says Sarah. "I thought this would be a great way to better understand some of the technologies that they're using in the field nowadays, as well."

For more information about the HYRS Program, please check the AHFMR Web site at www.ahfmr.ab.ca and click on "For Students".

Canadian Publications Agreement #40064910

Physicians: please place in your patient waiting rooms.

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